

# REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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In re Application of <i>Weiss et al</i>	
Application Number <i>08/149,508</i>	Filed <i>Nov 9, 1993</i>
Art Unit	Examiner

Paper No. *#16*

Assistant Commissioner for Patents  
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. \_\_\_\_\_, page \_\_\_\_\_, line \_\_\_\_\_,  
United States Patent Number *6294346*, column \_\_\_\_\_, line \_\_\_\_\_, or  
an International Application which was filed on or after November 29, 2000 and which  
designates the United States, WIPO Pub. No. \_\_\_\_\_, page \_\_\_\_\_, line \_\_\_\_\_.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or  
1.14(e)(2)(i), i.e., Application No. \_\_\_\_\_, paper No. \_\_\_\_\_, page \_\_\_\_\_, line \_\_\_\_\_.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

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US006294346B1

(12) **United States Patent**  
Weiss et al.

(10) **Patent No.:** US 6,294,346 B1  
(45) **Date of Patent:** Sep. 25, 2001

(54) **USE OF MULTIPOTENT NEURAL STEM CELLS AND THEIR PROGENY FOR THE SCREENING OF DRUGS AND OTHER BIOLOGICAL AGENTS**

(75) **Inventors:** Samuel Weiss; Brent Reynolds, both of Calgary (CA); Joseph P. Hammang; E. Edward Baetge, both of Barrington, RI (US)

(73) **Assignee:** Neurospheres Holdings, Ltd., Alberta (CA)

(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** 08/484,406

(22) **Filed:** Jun. 7, 1995

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 08/385,404, filed on Feb. 7, 1995, now abandoned, and application No. 08/376,062, filed on Jan. 20, 1995, now abandoned, and application No. 08/359,945, filed on Dec. 20, 1994, now abandoned, and application No. 08/338,730, filed on Nov. 14, 1994, now abandoned, and application No. 08/311,099, filed on Sep. 23, 1994, now abandoned, and application No. 08/270,412, filed on Jul. 5, 1994, now abandoned, and application No. 08/149,508, filed on Nov. 9, 1993, now abandoned, which is a continuation-in-part of application No. 07/726,812, filed on Jul. 8, 1991, now abandoned, said application No. 08/961,404, is a continuation of application No. 07/961,813, filed on Oct. 16, 1992, now abandoned, which is a continuation-in-part of application No. 07/726,812, said application No. 08/376,062, is a continuation of application No. 08/010,829, filed on Jan. 29, 1993, now abandoned, which is a continuation-in-part of application No. 07/726,812, said application No. 08/359,945, is a continuation of application No. 08/221,655, filed on Apr. 1, 1994, now abandoned, which is a continuation of application No. 07/967,622, filed on Oct. 28, 1992, now abandoned, which is a continuation-in-part of application No. 07/726,812, said application No. 08/338,730, is a continuation-in-part of application No. 07/726,812, said application No. 08/311,099, is a continuation-in-part of application No. 07/726,812, said application No. 08/270,412, is a continuation-in-part of application No. 07/726,812.

(51) **Int. Cl.<sup>7</sup>** ..... G01N 33/554; C12N 5/00

(52) **U.S. Cl.** ..... 435/7.21; 435/368; 435/377; 435/375

(58) **Field of Search** ..... 435/7.21, 368, 435/378, 377, 375

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,753,635	6/1988	Sagen et al.	604/49
4,980,174	12/1990	Sagen et al.	424/563
5,082,670	1/1992	Gage	424/520
5,175,103	12/1992	Lee et al.	435/172.3
5,411,883	5/1995	Boss et al.	435/240.2
5,589,376 *	12/1996	Anderson et al.	435/240.2
5,612,211	3/1997	Wilson et al.	435/378

**FOREIGN PATENT DOCUMENTS**

0 233 838 8/1987 (EP)

89/03872	5/1989	(WO)
90/06757	6/1990	(WO)
91/02003	2/1991	(WO)
91/09936	7/1991	(WO)
91/17242	11/1991	(WO)
93/01275	1/1993	(WO)
93/09802	5/1993	(WO)
94/03199	2/1994	(WO)

**OTHER PUBLICATIONS**

Cattaneo et al., "Proliferation and differentiation of neuronal stem cells regulated by nerve growth factor," *Nature*, 347:762-765 (1990).

Lin et al., "GDNF: A Glial Cell Line-Derived Neurotrophic Factor Midbrain Dopaminergic Neurons," *Science*, 260:1130 (1993).

Rosenberg et al., "Grafting genetically modified cells to the damaged brain: restorative effects of NGF expression," *Science*, 242:1575-1578 (1988).

Nurcombe et al., "Developmental Regulation of Neural Response to FGF-1 and FGF-2 By Heparan Sulfate Proteoglycan," *Science*, 260:103-106 (1993).

Brickman et al., "Heparan Sulfates Mediate the Binding of Basic Fibroblast Growth Factor to a Specific Receptor on Neural Precursor Cells," *Journal of Biological Chemistry*, 270(42):24941-24948 (1995).

Blakemore et al., "Extensive Oligodendrocyte Remyelination Following Injection of Cultured Central Nervous System Cells into Demyelinating Lesions in Adult Central Nervous System," *Developmental Neuroscience*, 10:1-11 (1988).

(List continued on next page.)

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(57) **ABSTRACT**

A culture method for determining the effect of a biological agent on multipotent neural stem cell progeny is provided. In the presence of growth factors, multipotent neural stem cells are induced to proliferate in culture. The multipotent neural stem cells may be obtained from normal neural tissue or from a donor afflicted with a disease such as Alzheimer's Disease, Parkinson's Disease or Down's Syndrome. At various stages in the differentiation process of the multipotent neural stem cell progeny, the effects of a biological agent, such as a virus, protein, peptide, amino acid, lipid, carbohydrate, nucleic acid or a drug or pro-drug on cell activity are determined. Additionally, a method of screening the effects of biological agents on a clonal population of neural cells is provided. The technology provides an efficient method for the generation of large numbers of pre- and post-natal neural cells under controlled, defined conditions. The disclosed cultures provide an optimal source of normal and diseased neural cells at various developmental stages, which can be screened for potential side effects in addition to testing the action and efficacy of different biological agents.